

REMARKS

Claims 16-33 are pending in the application. All claims stand rejected. No claims are allowed.

The Brief Description of Figures 4-6 has been amended in the specification to indicate that the respective data was obtained on Form-I of 5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]methoxy]benzyl]thiazolidine-2,4-dione potassium salt, rather than the novel crystalline Form of the compound. Support for the amendment can be found at, *e.g.*, page 7, lines 22-29 of the specification as originally filed. No new matter has been introduced by these amendments.

Claims 16-28 and 31-33 have been amended to more clearly describe and distinctly claim the subject matter the Applicants consider their invention. In particular, claims 16 and 20 have been amended to correct a minor transcriptional error in the structure of the formula that occurred during submission of the Preliminary Amendment on September 13, 2004. Support for the amendment can be found in the claims as originally filed and at, *e.g.*, p.1, line 13 and p. 6, line 13 of the specification as originally filed. Claims 24 and 26 have been amended to more clearly specify which organic solvent is intended. Support for the amendment can be found at, *e.g.*, Examples 2-12 of the specification as originally filed. No new matter has been introduced by these amendments.

Reconsideration and allowance of claims 16-33 in view of the amendments above and the remarks below are respectfully requested.

Claim Rejections – 35 U.S.C. § 102

Claims 16-18, 20-24 and 28-33 are rejected under 35 U.S.C. § 102(b) as allegedly inherently anticipated by Chebiyyam et al. (WO 00/15638; hereinafter “Chebiyyam”). Applicants respectfully traverse this basis for rejection.

Claims 16-18 and 20-22 are directed to new polymorphic forms of 5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]methoxy]benzyl]thiazolidine-2,4-dione potassium salt having specifically recited solid-state characteristics. Amended

claims 23-24 recite a process for preparing the novel crystalline forms of the present invention, which comprises dissolving 5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]methoxy]benzyl]thiazolidine-2,4-dione potassium salt in an organic solvent, heating to about 60-75°C, adding potassium tertiary butoxide dissolved in an organic solvent at a temperature of 40-55°C, cooling the solution to room temperature, and recovering crystalline Form-I of 5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]methoxy]benzyl]thiazolidine-2,4-dione potassium salt.

Polymorphs arise when molecules of a compound are arranged in the solid state in distinct ways. By varying the temperature of the solution and using different solvents, different polymorphs can be formed. Although identical in chemical composition, polymorphs can have very different properties. Polymorphs are distinguishable by various analytical techniques, especially X-ray powder diffraction patterns.

The Examiner contends that Example 40 of Chebiyyam discloses a similar process using the solvent of xylene:MeOH, heating at temperature of about 80°C, and adding potassium t-butoxide. According to the Examiner, because the disclosed process is similar to the claimed process, it is presumed that the same crystal as recited in claims 16-18 and 20-22 would be obtained.

According to the MPEP § 2131:

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 638, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)).

Contrary to the Examiner's contention, the similar process of Example 40 of Chebiyyam does not disclose each and every limitation as set forth in claims 16-18 and 20-24. Furthermore, Chebiyyam describes, in Example 40, a method for preparing 5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]methoxy]benzyl]thiazolidine-2,4-dione potassium salt. There is no teaching in Chebiyyam of polymorphs, let alone the particular polymorphs disclosed and claimed in the instant application. As such, Chebiyyam cannot anticipate the claimed invention.

Contrary to the Examiner's assertion, the new crystalline form of claims 16-18 is not inherently obtained from the process disclosed in Example 40 of Chebiyyam. According to the MPEP § 2112:

To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (emphasis added).

*See also Ex parte Havens*, Appeal No. 2001-0091 for Application No. 08/732,254, now US 6,452,007 B1 (BPAI 2001). ("The examiner has provided no evidence or scientific reasoning to show that the delavirdine mesylate disclosed and claimed [in the prior art reference] is in the [claimed] crystal form. Therefore, the examiner has not made out a *prima facie* case of anticipation by inherency.").

Even assuming it was crystalline, the undisclosed form of 5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]methoxy]benzyl]thiazolidine-2,4-dione potassium salt made in Example 40 of Chebiyyam cannot be both the new crystalline form of claims 16-18 and polymorphic form I of claim 23. This in itself establishes that the requisite solid-state characteristics for the new crystalline form of 5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]methoxy]benzyl]thiazolidine-2,4-dione potassium salt are not necessarily present in the process described in Chebiyyam, and the Examiner has failed to make out a *prima facie* case for inherent anticipation. In fact, the Examiner provides no evidence whatsoever that the practice of Example 40 of Chebiyyam yields either the new crystalline form or polymorphic form I of 5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]methoxy]benzyl]thiazolidine-2,4-dione potassium salt. Therefore, Applicants submit that Chebiyyam does not anticipate claims 16-18 and 20-24 of the instant

Accordingly, Applicants submit that Chebiyyam does not anticipate claims 16-18 and 20-24 of the instant application, and reconsideration of this basis for rejection is respectfully requested.

Claims 28-33 are directed to pharmaceutical compositions of the polymorphic forms of the present invention and method of treatment using said polymorphic forms. Since Chebiyyam does not teach the crystalline forms of the present invention, there cannot be any teaching of the limitations of claims 28-33. Thus, Applicants submit that claims 28-33 are not anticipated under §102(b) by the prior art of record, and reconsideration of this rejection is respectfully requested.

#### Claim Rejections – 35 U.S.C. § 103

Claims 19 and 25-27 are rejected under 35 U.S.C. § 103(a) as obvious over Chebiyyam et al. The Examiner contends that the process disclosed in Example 40 of Chebiyyam differs from the process recited in claim 19 by having the solvent of xylene: MeOH, and not xylene:acetonitrile, and differs from the process recited in claims 25-27 by different temperature range. According to the Examiner, xylene, MeOH and acetonitrile are known organic solvents used in many reaction schemes, and would be within the level of the skilled chemist to select to achieve desirable yield. Likewise, according to the Examiner, the difference in temperature range would also be within the level of the skilled chemist to select to obtain optimum yield. Applicants respectfully traverse this basis for rejection.

According to the MPEP § 2143:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the

claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

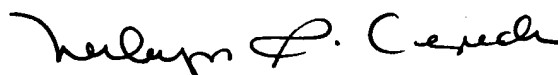
Claims 19 and 25-27 are directed to a method of new crystalline forms of 5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]methoxy]benzyl]thiazolidine-2,4-dione potassium salt having the specific solid-state characteristics recited in claims 16 and 20. As discussed above, Chebiyyam is silent as to the crystalline forms of 5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]methoxy]benzyl]thiazolidine-2,4-dione potassium salt.

Here, regardless of whether the difference in solvents or temperature range would be within the level of skill in the art to obtain optimal yield, the Examiner has pointed to nothing in Chebiyyam, or in the knowledge generally available at the time, that would have suggested to one skilled in the art a reasonable likelihood of success of obtaining the particular new crystalline forms of 5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]methoxy]benzyl]thiazolidine-2,4-dione potassium salt recited in claims 19 and 20 and having the specific solid-state characteristics recited in claims 16-27. It is well known in the art that the choices of solvent and temperature used in a crystallization process play a critical role in the formation of a particular crystalline form, and which form will be ultimately produced is unpredictable. This is evidenced by the fact that in the instant application the new crystalline Form of 5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]methoxy]benzyl]thiazolidine-2,4-dione potassium salt is obtained in Example 1 using a mixture of acetonitrile and xylene at 75-80° C, while polymorphic Form-I of 5-[4-[[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]methoxy]benzyl]thiazolidine-2,4-dione potassium salt is obtained in Examples 2-13 using different solvents at different temperatures. Accordingly, Applicants submit that no *prima facie* case of obviousness has been made out for claims 19 and 25-27 of the instant application, and reconsideration of this basis for rejection is respectfully requested.

In view of the foregoing Amendment and Response, it is believed that claims 16-33 are now in condition for allowance, early notice of which would be appreciated. Applicants request the Examiner to telephone the undersigned attorney should the Examiner have any questions or comments, which might be most expeditiously handled

by a telephone conference. Other than the time extension fee, no fee is deemed necessary in connection with the filing of this Response. If any fee is required, however, authorization is hereby given to charge the amount of such fee to Deposit Account No. 50-3221.

Respectfully submitted,



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